

LETTERS TO THE EDITOR

Does Glucocorticoid Dysregulation Contribute to the Link Between Cigarette Smoking and Insulin Resistance?

In a recent issue of the *Journal*, Drs. Reaven and Tsao (1) discussed the association between cigarette smoking and insulin resistance, endothelial dysfunction, and dyslipidemia. They assert that insulin resistance may be a key mechanism by which smoking increases the risk of atherosclerotic cardiovascular disease. We agree with this assertion and suggest that elevated glucocorticoid tone may be an important link between cigarette smoking and insulin resistance.

Cigarette smokers may have higher serum cortisol levels than nonsmokers of similar age and body mass index (BMI) (2). Furthermore, elevated afternoon cortisol levels appear to fall after smoking cessation (3). Although the mechanisms for altered glucocorticoid homeostasis in smokers remains to be defined, it is well known that long-term glucocorticoid exposure causes visceral obesity and carbohydrate insulin resistance, and it is also likely that interindividual variation in glucocorticoid homeostasis contributes to insulin resistance in the general population (4). Thus, it is plausible that chronically dysregulated glucocorticoid homeostasis in smokers may have adverse effects on glucose metabolism and body fat distribution.

Visceral obesity—even when BMI is normal or low—is associated with insulin resistance and increased cardiovascular risk, and cigarette smokers may have a two-fold greater risk of developing this anthropometric phenotype compared with nonsmokers (5). This observation provides further circumstantial evidence that altered glucocorticoid homeostasis in smokers might have chronic consequences. In summary, the link between smoking and insulin resistance may be at least partly explained by elevated activity of the stress hormone cortisol.

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REPLY

We appreciate the support of Drs. Girod and Brotman for our hypothesis that the increased prevalence of insulin resistance and hyperinsulinemia in cigarette smokers may play a central role in the dyslipidemia, endothelial dysfunction, and increased cardiovascular disease associated with tobacco use. However, we are not as persuaded as they seem to be that the link between cigarette smoking and insulin resistance is mediated via higher serum cortisol levels, secondary to smoking-induced visceral obesity. For example, in our initial study (1) we documented the presence of insulin resistance and compensatory hyperinsulinemia in smokers as compared with nonsmokers, matched for age, gender, family history of diabetes, alcohol consumption, level of physical activity, body mass index (BMI), and the ratio of waist-to-hip girth (WHR). Subsequent studies have also demonstrated that insulin resistance/hyperinsulinemia can be demonstrated in smokers independently of either BMI or WHR, and in two of these studies (2,3) it was shown that the enhancement of insulin sensitivity occurring with smoking cessation can be seen despite weight gain.

Conversely, in none of these studies was body fat distribution quantified by computerized tomography. Thus, the suggestion that the insulin resistance of smokers is due to a redistribution of body fat, with a relative increase in visceral obesity, cannot be dismissed. However, it should be noted that the observation of a smoking-related change in body fat distribution was made in only one ethnic group (4), and individuals of Korean ancestry may not be characteristic of the world at large. Furthermore, direct measurements of visceral obesity were not performed, and the suggestion that visceral obesity was present was based entirely on evidence that the ratio of WHR/BMI was increased in smokers. It should also be noted that the two-fold risk to have the highest WHR/BMI ratio was limited to 4.7% and 3.8% of the male and female smokers, respectively.

Finally, the relationship between visceral obesity and insulin resistance is a complex one. Perhaps the most revealing example of this is the recent report by Seppala-Lindroos et al. (5), showing with proton spectroscopy and magnetic resonance imaging in healthy volunteers that hepatic fat content was unrelated to amount of visceral fat, whereas the amount of fat in the liver, not visceral fat, was closely related to a variety of abnormalities associated with insulin resistance, including fasting hyperinsulinemia. In contrast, the formulation advanced by Girod and Brotman is certainly testable, and despite our skepticism it is worthy of experimental verification. Most importantly, the correspondents' letter should serve, along with our original comments, to indicate the need for a better understanding of the relationship between cigarette smoking and the wide variety of metabolic factors with which it is associated.

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Clopidogrel Versus Ticlopidine After the Placement of Coronary Artery Stents

In a study published recently in *JACC*, Mueller et al. (1) compared treatment with clopidogrel and aspirin to ticlopidine and aspirin in patients undergoing coronary stent placement. Both drugs were started after the procedure and continued for four weeks. Ticlopidine was given as a 500-mg loading dose followed by 250 mg twice daily thereafter; however, clopidogrel was given without loading: 75 mg daily. The results suggested that clopidogrel was inferior to ticlopidine in terms of cardiovascular mortality. In other studies involving clopidogrel, a loading dose of 300 mg was given initially followed by 75 mg daily thereafter (2,3). A loading dose of 300 mg of clopidogrel is needed in order to achieve timely platelet inhibitory effect (4). The lack of clopidogrel loading clearly delays the effect of clopidogrel and, therefore, may cause a higher thrombotic stent occlusion (TSO) rate (the TSO rate was not reported by Mueller et al.). Use of a clopidogrel loading dose in this instance may show clopidogrel not to be inferior to ticlopidine (3).

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REPLY

We fully agree with Dr. Rott that the lack of a loading dose of clopidogrel is an important issue in interpreting our data. After completion of our study, two major clinical trials, Clopidogrel for the Reduction of Events During Observation (CREDO) (1) and ISAR-REACT (2), were reported that highlight the need for a loading dose of clopidogrel. In CREDO, the best clinical outcome was seen in those patients who achieved the full antiplatelet effect of clopidogrel at the time of intervention, which was 6 h after a loading dose of 300 mg. Based on clinical observations (3) and ex vivo analysis of platelet function (4), the ISAR-REACT trial used an even higher loading dose of clopidogrel, 600 mg, which enables the full antiplatelet effect of clopidogrel within 2 h (4). With this loading scheme, the antithrombotic efficacy in patients undergoing elective interventions could not be further improved even with abciximab, as shown by the composite 30-day end point of death, myocardial infarction, and urgent revascularization (2).

In light of these new findings, we cannot exclude that the results of our trial, as well as those of other trials suggesting inferiority of clopidogrel compared with ticlopidine (5), would have been different had an appropriate loading dose been used. Notably, a high loading dose may overcome the other potential explanation of our findings, which is the interference of statins. Although the issue has not been completely settled, preliminary reports indicate that attenuation of the antiplatelet effect by statins is not detectable after a 600-mg loading dose (6).

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